REMARKS

The Official Action dated March 29, 2011 has been carefully considered. By present Amendment claim 15 is amended to correct an inadvertent typographical error..."iopolymer" is clearly intended to be "biopolymer" based on the context of the claims and the teachings of the specification. Since the change does not involve new matter, entry is believed warranted and is respectfully requested.

Claims 1-3, 13, and 15-22 remain pending and under examination.

35 USC §102

Claims 1-2, 13, and 15-22 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Application Publication No. 20020045167 to Agris ("Agris"). Generally the Examiner asserts that Agris teaches, throughout the document and especially the abstract and paragraphs 0002-0006 and Figure 11, antibodies specific for oligonucleotide protecting groups applied toward detecting incomplete deprotection on microarrays. Specifically the Examiner alleges that Agris suggests that the antibodies may be used on chips such as developed by Fodor, etc., which are made by synthesizing a plurality of biopolymer species on an array from monomeric or oligomeric nucleotide building blocks comprising detectable protecting groups coupled directly to amino groups of the nucleotide building blocks, wherein the detectable protecting groups remain coupled until synthesis of the biopolymer array is complete, as set forth in claim 1a. According to the Examiner, in Figure 8, Agris takes a step to cleave detectable protecting groups such as Bz and ipr-Pc, as set forth in claim 1b; with said antibodies, determine the degree of deprotection by detecting any of Bz and ipr-Pac remaining on an array after cleavage, as set forth in claim 1c; and re-deprotect until the detectable protecting groups are no longer detected, indicating that complete deprotection is achieved, as set forth in claim 1d. Antibody binding

does not destroy the oligonucleotides as set forth in the second wherein clause of claim 1. Further according to the Examiner, Argis indicates the method may be used with fluorescent protecting groups such as fluorenylmethoxycarbonyl, reading on claim 2, and the oligonucleotide reads on the nucleic acid (elected species) of claim 13.

This rejection is traversed and reconsideration is respectfully requested.

Claim 1 is directed to a quality control method for **achieving complete deprotection** of protected reactive groups in on-chip synthesis of a biopolymer array. The method comprises: (a) synthesizing a plurality of biopolymer species on an array from monomeric or oligomeric nucleotide building blocks comprising detectable protecting groups coupled directly to amino groups of the nucleotide building blocks, wherein the detectable protecting groups remain coupled until synthesis of the biopolymer array is complete, (b) taking one or more steps to cleave the detectable protecting groups, (c) determining a degree of deprotection by detecting any of the detectable protecting groups remaining on the array after cleavage, and (d) **repeating steps (b) and (c) until the detectable protecting groups are no longer detected, indicating that complete deprotection is achieved**. The quality control method is performed entirely on-chip and the synthesized biopolymer array not destroyed by practice of the quality control method. Underlining is added to emphasize points which pertain to this traversal. Notably, the instant invention provides a chip where deprotection is complete, and the method involves iteration of the steps of deprotecting and assessing deprotection until deprotection is complete...all on the chip, and all without destroying the synthesized biopolymer. A fully functional, completely deprotected chip is the end result.

Agris, on the other hand, provides a method for compensating for insufficiency of deprotection. Agris never teaches or suggests a method for completely deprotecting a

biopolymer synthesized on the chip. Agris provides an antibody that differentially detects protected over unprotected oliogonucleotides. Use of the antibody allows the clinician to determine the sufficiency of deprotection and a means to correct for any deficiency by generating a "record" or "indicia" of the degree of insufficiency, which thereafter maybe used in data analysis to compensate for the insufficiency.

Critically then, Agris teaches determining degree of deprotection for purposes of compensating, while the instant methods determine degree of deprotection in order to completely eliminate protecting groups from the chip.

The Examiner asserts that Agris suggests repeating the deprotection and detection steps until complete deprotection is achieved, and points to paragraph [0162] for this alleged teaching. Applicants respectfully disagree. Careful inspection of this paragraph reveals that it actually teaches a method whereby steps of providing an antibody that specifically binds to a protected oligo (step (b) from prior paragraph), and the step of contacting the oligo array to the antibody to determine presence of insufficient deprotection (step (c) from prior paragraph) may be repeated *"with a different antibody on each repetition, so that a plurality of different protecting groups which may be present on the oligonucleotides in the array may be detected"*. Agris is NOT suggesting that steps of determining deprotection and deprotection itself be repeated until deprotection is complete. In fact, Agris never teaches or suggests any additional deprotection steps once insufficiency is determined. The Agris embodiment discussed in paragraph [0162] is merely with respect to determining a distinct indicia for each type of protecting group which may be present, not for achieving complete deprotection of a given group where deprotection is found to be insufficient.

The Examiner further asserts that Example 10 illustrates subsequent deprotection of detected protecting groups. However, Applicants note that Example 10 is not carried out as part of on-chip synthesis; rather, Example 10 describes the investigation of commercially available oligonucleotides for the presence of remnant protecting groups. There is no suggestion that these groups be removed and/or that a second determination of sufficiency be conducted. The authors suggest preparation of a quality control report for purposes of informing an end user of elongation and deprotection status of the product so that correction may be incorporated into the analysis. Agris never teaches or suggests complete deprotection of any chip, and never suggests additional deprotection beyond a determination of insufficiency. According to the instant invention, on the other hand, quality control is carried out as part of the synthetic protocol to ensure that the resulting array does not bear protecting groups and may be used without the need for analytical corrections. Indeed, it may be said that the instant invention renders the invention of Agris unnecessary.

One advantage of the instant invention is that the steps of deprotecting and determining may be repeated as often as desired or required to achieve complete deprotection. However, repetition of these steps cannot be realized by the methods of Agris. Agris cannot be fairly assessed as enabling the instant invention, since Agris fails to teach or suggest any additional deprotection subsequent to a determination that insufficient deprotection exists. Agris cannot provide completely deprotected chips unless by happenstance a chip emerges completely deprotected upon synthesis.

Moreover, Applicants assert that an attempt to achieve complete deprotection by using the antibodies of Agris would impose many degrees of complexity on the synthetic protocol. Even if the antibodies were labeled with, e.g., a fluorescent label, an environment providing for

binding of the antibody while avoiding non-specific binding on the surface, such as by use of a blocking step described in paragraph [0198], step (d), would be required.

Anticipation under 35 U.S.C. § 102(b) requires the disclosure in a single prior art reference of each element of the claims under consideration, *Alco Standard Corp. v. TVA*, 1 U.S.P.Q.2d 1337, 1341 (Fed. Cir. 1986). Agris cannot be said to anticipate the instant invention as defined by the independent claims since Agris fails to teach or suggest methods for achieving complete deprotection of protected reactive groups in on-chip synthesis of a biopolymer array. Agris fails to teach method step (d) according to claim 1 of the instant invention whereby steps (b) and (c) are repeated until complete deprotection occurs. Agris fails to teach all the elements of the instant claims.

To serve as an anticipating reference, the reference must enable that which it is asserted to anticipate. "A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003). Agris teaches a method of screening bioarrays for insufficient deprotection. Agris teaches methods of compensating for deficient deprotection using mathematical indicia in data analysis. Agris never suggests additional steps of deprotecting with respect to an insufficiently deprotected chip. Agris never, therefore, contemplates or describes how this might occur given that cleavage of antibody-bound oligo's presents another layer of blocking and unblocking with respect to the antibody itself, and with respect to nonspecifically bound antibody.

For these reasons independent claim 1 and dependent claims 13 and 15-22 are novel under 35 U.S.C. §102 over Agris. Reconsideration is respectfully requested.

35 USC §103

Claims 1-2, 13, 15-22 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agris in view of Nagaich et al (1989 Nucleic Acids Research 17:5125-5134) ("Nagaich"). Specifically, Agris is applied as set forth above. The Examiner notes that Agris fails to teach or suggest stilbene protecting groups as recited in instant claim 3. Nagaich is applied for teaching stilbene protecting groups for cytidine, adenine and guanine nucleosides, therefore reading on at least this element of claim 3. The Examiner concludes that it would have been prima facie obvious for one of ordinary skill in the art at the time the claimed invention was made to utilize the stilbene protecting groups of Nagaich in making microarrays and conducting deprotection in accordance with Agris.

This rejection is traversed and reconsideration is respectfully requested.

Independent claim 1 is set forth in detail above. Notably, claim 1 is directed to a method for achieving complete deprotection of protecting groups during on-chip synthesis of a biopolymer array and requires, inter alia, steps for deprotection and determining deprotection which may be repeated in tandem until complete deprotection is achieved. To the best of Applicants knowledge, this is the simplest and most efficient method developed for providing biopolymer arrays that have been completely deprotected upon completion of synthesis.

The primary reference, on the other hand, is directed to methods of screening biopolymer arrays for insufficient deprotection. When degree of deficiency is determined, rather than repeating a deprotection protocol, Agris teaches calculation of an index reflecting the degree of protection and used to correct data analysis. Agris teaches compensation, whereas the instant methods negate the need for compensation.

Further, the methods of Agris cannot be readily adapted to provide the methods of the instant invention. At a minimum, Agris requires the binding of a different labeled antibody for each protecting group. This must be done in tandem rather than parallel steps unless the label for each antibody type is different. Further, nonspecific antibody binding must be controlled (as discussed by Agris) by blocking or washing chemistries, all of which would add layers of complexity to the overall protocol. It is unclear and one would have conduct undue experimentation in order to determine whether and how one could run subsequent deprotection steps on oliogonucleotides bound by labeled antibody.

The secondary reference Nagaich is inapposite on this point and fails to overcome the deficiencies of the primary reference with respect to the independent claim. Nagaich relates to oliognucleotide synthesis, but focuses on selective protection and deprotection procedures and provides an improved protecting group. Nagaich does not address problems or challenges/solutions unique to on-ship synthesis and quality control with respect to degree of deprotection.

To establish prima facie obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art, *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). Applicants assert, as argued above, that Agris in view of Nagaich fails to teach or suggest methods for achieving completely de-protected biopolymer arrays and specifically fails to teach or suggest methods where the quality control with respect to deprotection is achieved on the chip as part of the synthetic process, without destroying any part of the biopolymer array.

In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 U.S.P.Q.2d 1481, 1489 (Fed. Cir. 1997). Further, the combination of Agris and Nagaich fails to

teach or suggest how one might accomplish on-chip quality control assurance and provision of completely deprotected biopolymer arrays using the determination technology of labeled antibody as provided by Agris. The methods of the instant claims require that after determination of insufficient deprotection, the chip is subject to further deprotection chemistries. To achieve this efficiently and with a minimum of complexity Applicants have developed and/or selected particular protecting chemistries and strategies. The Examiner fails to explain how the combination of Agris and Nagaich could possibly achieve the instant methods since deprotecting anti-body bound oligos without consideration of this need during the selection of protecting groups is not contemplated or enabled.

Dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious. *Hartness Int'l, Inc. v. Simplimatic Eng'g Co.*, 819 F.2d 1100, 1108, 2 USPQ2d 1826, 1831 (Fed. Cir. 1987). Hence, independent claim 1 and all claims dependent therefrom, including claim 3, are nonobvious and patentable over Agris in view of Nagaich. Reconsideration is respectfully requested.

35 USC §112

Claims 15-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically the Examiner notes that the term "iopolymer" as recited in claim 15 is indefinte. Applicants acknowledge and appreciate the Examiner bringing attention to the inadvertent typographical error present in claim 15. Applicants submit that based on context and tangential disclosure it is clear that the letter "b" was mistakenly omitted from the term

"biopolymer." Applicants have corrected by present Amendment, thereby mooting the rejection. Reconsideration is therefore respectfully requested.

Conclusion

Applicants submit that the foregoing is a comprehensive and persuasive response to the rejections under 35 U.S.C. §§102, 103 and 112 as set forth in the March 29 office action. Nonetheless if the Examiner perceives any remaining issue(s) which may be readily resolved, he is invited to contact Applicants through their agent listed below. Otherwise reconsideration and an early allowance are respectfully requested.

Sincerely,

/Denise M. Everett/

Denise M. Everett
Reg. No. 47,552
Dinsmore & Shohl
Counsel for Applicants